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16. ABSTRACT

Cancer risk from exposure to benzene for a working lifetime was estimated from data obtained in studies with rodents. Cancers of the Zymbal gland and the blood-forming system were selected as endpoints for the assessment because of their consistent occurrence. The combined metabolites were judged from toxicological data to be the best representative of the reactive agent. Because of similarity in the percentages of lifetime exposed in the rodent studies and in the occupational setting, the amount metabolized/day as a result of exposures 5 days a week for a lifetime was judged to be an appropriate dose paradigm for this assessment. Derived Michaelis-Menton constants were used to convert the doses of combined metabolites from the pharmacokinetic studies to the doses used in the bioassays. Scaling across species was based on allometric relationships. Experimental data were used to scale doses across species with body weight ratios raised to the exponents of 0.74 for the inhalation route and 1.0 for the oral route. The occupational lifetime cancer risk estimated from rodent data was 6 to 14 cases/1000 workers, which is consistent with the 9.5 to 174 leukemia cases/1000 estimated by others from epidemiological data. Implications of these estimates and uncertainties associated with making them are discussed.

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Pharmacokinetically Based Risk Assessment of Workplace Exposure to Benzene[1]

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Cancer risk from exposure to benzene for a working lifetime was estimated from data obtained in studies with rodents. Cancers of the Zymbal gland and the blood-forming system were selected as endpoints for the assessment because of their consistent occurrence. The combined metabolites were judged from toxicological data to be the best representative of the reactive agent. Because of similarity in the percentages of lifetime exposed in the rodent studies and in the occupational setting, the amount metabolized/day as a result of exposures 5 days a week for a lifetime was judged to be an appropriate dose paradigm for this assessment. Derived Michaelis–Menton constants were used to convert the doses of combined metabolites from the pharmacokinetic studies to the doses used in the bioassays. Scaling across species was based on allometric relationships. Experimental data were used to scale doses across species with body weight ratios raised to the exponents of 0.74 for the inhalation route and 1.0 for the oral route. The occupational lifetime cancer risk estimated from rodent data was 6 to 14 cases/1000 workers, which is consistent with the 9.5 to 174 leukemia cases/1000 estimated by others from epidemiological data. Implications of these estimates and uncertainties associated with making them are discussed. © 1989 Academic Press, Inc.

INTRODUCTION

Estimates of cancer risk related to occupational exposure to benzene as calculated by several investigators were summarized by Infante (1987). The estimated risks of leukemia for a working lifetime (40 to 45 years) ranged from 9.5 to 174 cases/1000 workers exposed at 10 ppm and 5 to 14 cases/1000 workers exposed at 1 ppm.

Sufficient animal cancer response data and pharmacokinetic data on benzene have recently become available so that it is of interest to compare the risk estimated from

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responses in animal studies to the risk estimated from epidemiological data. The purpose of this investigation is to examine pharmacokinetic information regarding route-to-route and species-to-species extrapolation, with the ultimate consideration being the usefulness of these techniques in the assessment of cancer risk resulting from occupational exposure. This effort should not be misunderstood as a replacement of risk assessment based on occupational epidemiological studies, but rather its primary purpose is to determine the utility of the techniques when only animal data are available.

Using data from animal studies to estimate human cancer risk associated with exposure to a chemical requires mathematical extrapolation from generally high experimental doses and the corresponding observed animal responses to levels lower than the experimental doses and the associated risk (probability of response minus background). The doses and response data are fitted to a curve, and the additional risk at a lower dose is estimated by extrapolation. The "dose" used in these calculations is assumed to be the effective dose. The applied dose is, however, frequently used and is expressed as the concentration of the chemical in the environment or the amount that was administered. In the case of a procarcinogen, a better estimate would be the amount of the ultimate carcinogen resulting from the applied dose. A still better estimate of the effective dose would be the amount of the reactive agent(s) reaching the target tissue.

In the assessment of risk based on animal data, the selection of the tumor endpoint is most frequently based on the conservative approach of using the endpoint resulting in the highest risks (USEPA, 1986). The resulting estimated risks are for any cancer, not for cancer of a particular type or at a specific site.

Appropriate low-dose extrapolation requires consideration of the dose of reactive molecule or molecules involved with tumor initiation, promotion, and progression or other mechanisms or stages; application of pharmacokinetics; scaling across species; and in some cases use of data from exposures by one route to estimate risk when exposure takes place by a different route.

The doses may be scaled across species to account for differences in size, metabolic rate, or other anatomical or physiological factors. In many instances, differences in the durations of exposure and the percentages of lifetime exposed must be considered. In this assessment, the maximum occupational scenario was chosen because it is similar to the percentage of lifetime that rodents are usually exposed in inhalation bioassays. We used a target exposure concentration near the experimental range to reduce controversy about the choice of risk assessment extrapolation model, as the mathematical models for extrapolation tend to predict similar risks near the experimental exposure range. For illustrative purposes, the multistage model was used, with the polynomial degree selected by the program for best fit (Howe *et al.*, 1986).

SELECTION OF TUMOR ENDPOINTS

Tumors of the Zymbal gland are the most consistent tumor type in bioassays of benzene with rodents, whereas neoplasms of the blood and blood-forming organs (leukemia) are the most frequently reported cancers in humans associated with occupational benzene exposure. In some studies with mice, tumors of the hematopoietic system were found, but in only female mice after exposures to airborne benzene (Sny-

der *et al.*, 1980; Cronkite *et al.*, 1984) and in only male mice after oral dosing (NTP, 1986). The Zymbal gland tumor was a consistent tumor in rats and mice in the National Toxicology Program (NTP) oral bioassay. Maltoni and Scarnato (1979) also reported increased Zymbal gland carcinomas among female Sprague–Dawley rats receiving benzene by gavage 4 to 5 days a week for 52 weeks at daily doses of 250 and 50 mg/kg/day. In addition, Maltoni *et al.* (1982) reported an increased incidence of Zymbal gland tumors among male as well as female rats given 500 mg/kg orally for 104 weeks. These authors also confirmed the induction of Zymbal gland carcinomas in Wistar rats and in Swiss mice given gavage doses of 500 mg/kg. Zymbal gland carcinomas were reported in inhalation studies from two different laboratories (Maltoni *et al.*, 1982; Snyder *et al.*, 1984).

We chose the Zymbal gland tumor endpoint because of consistency across animal species, although assessment of human risk from this endpoint will not estimate an organ-specific tumor response. The incidence of the Zymbal gland tumors in the NTP oral-dose bioassays was used in the present assessment mainly because of the more complete supporting data provided in the NTP (1986) report. The Zymbal gland tumor response resulting from exposure to airborne benzene reported by Maltoni *et al.* (1982) was used for comparison. For data on tumors of blood-forming organs, we selected the bioassays performed by Snyder *et al.* (1980) because, unlike in several other studies, the benzene inhalation exposure covered most of the rodent lifetime.

SELECTION OF REACTIVE AGENT

The specific reactive metabolites responsible for the toxicity to bone marrow are unknown (Rusch *et al.*, 1977; NTP, 1986); however, there are several likely candidates, including hydroquinone and catechol. Phenol, another benzene metabolite, is a promoter and weak initiator in the two-stage, mouse skin-painting model (Boutwell and Bosch, 1959), but it is not generally regarded as a likely causative metabolite for the bone marrow toxicity. Indeed, a combination of these metabolites has been suggested as the cause of the bone marrow toxicity. Eastmond *et al.* (1987) showed that benzene-induced myelotoxicity can be produced in mice by a combination of phenol and hydroquinone. In addition, the recent information of an effect of benzene on the immune system (Aoyama, 1986) suggests that more than one mechanism of action may be involved in the tumorigenic action of benzene. Because the metabolites of benzene could act together in inducing cancer by one or more mechanisms, the total amount of benzene metabolized (milligram benzene equivalents metabolized) will be considered the reactive agent.

SELECTION OF DOSE PARADIGM

It is generally agreed that the metabolism of benzene varies little among species in a qualitative sense (Rusch *et al.*, 1977; NTP, 1986). The most significant variations are that the pig excretes only the glucuronide and the cat excretes only the sulfate as the conjugated form in the urine, whereas most species, including humans, excrete both of these conjugates (Berlin and Tunek, 1984).

The available data on the formation of summed benzene metabolites in humans are sparse. To estimate the effective occupational daily dose, it was assumed that a

70-kg man breathes 10 m^3 in an 8-hr workday and that 60% is metabolized. The resulting daily human-metabolized dose at an airborne concentration of 10 ppm (32.6 mg/m^3) is 196 mg. According to Rusch *et al.* (1977), 40% of inhaled benzene is expired unchanged, while NTP (1986) reported that the amount exhaled unchanged ranges from 12 to 70%. Since greater percentages are metabolized at lower doses, the 60% assumed to be metabolized is compatible with the findings of Nomiyama and Nomiyama (1974a,b), who reported that 30% of benzene inhaled at 52 to 62 ppm was retained.

The assumptions made concerning a maximum occupational exposure are as follows: worker exposure occurs 40 hr/week, 48 weeks a year (10 days vacation and 10 days holiday and sickness), for 45 years, and the total lifetime is 70 years. Thus, a maximum occupational lifetime exposure represents an exposure of only 14% of the total lifetime. Daily 6-hr exposures for 2 years result in exposure for 15% of the 28 months estimated by Solleveld *et al.* (1984) as the rodent lifetime. No correction is necessary for this slight difference in the percentages of lifetime represented by exposures of animals in bioassays and by maximum exposure in the workplace.

The investigations of Sabourin *et al.* (1987) provide a basis for exploration of route-related pharmacokinetics. They found a dose-related effect on the absorption and excretion of [^{14}C]benzene following both oral and inhalation treatment of male F344/n rats (288 g) and B6C3F1 mice (30 g). They used urinary plus fecal ^{14}C concentrations as an estimate of total benzene metabolite formed, as more than 95% of the urinary and fecal ^{14}C is in the water-soluble metabolites. The metabolite formation was not linearly related to dose. Sabourin *et al.* found that more than 97% of gavage doses administered at 0.5 to 150 mg/kg was absorbed. The percentage that was retained after a 6-hr exposure to airborne benzene was inversely proportional to the concentration, with about 50% being retained at 50 ppm. Nearly all the radioactivity appearing in the urine was collected within 24 hr after exposure, regardless of route. Because it would take about 6 hr for renal clearance to cause the appearance of the product in the urine, it was appropriately assumed that the metabolite formation was complete within 1 day in the rodents.

The results of Sabourin *et al.* (1987) were used to estimate the apparent Michaelis–Menton constants. The K_m and V_{max} obtained by the Lineweaver–Burk method are presented in Table 1. The calculated apparent V_{max} values are remarkably similar within species for both routes of exposure, but the differences between the routes is notable. Because the metabolites of benzene are the likely reactive molecular species, the milligram equivalents of benzene metabolized in 1 day can be used as a reasonable estimate of the effective dose. The Michaelis–Menton constants provide a means for estimating the milligram equivalents of benzene metabolized from the applied doses in the bioassays.

ACROSS SPECIES SCALING

In a recent review, Davidson *et al.* (1986) concluded that scaling was most frequently successful when body weight ratios were raised to the power of 0.67 (for surface area), the power of 0.75 (for metabolic rate), or the power of one (for body weight). Scaling by surface area or by metabolic rate gave similar results, whereas those obtained with scaling by body weight differed more from the results with scaling

TABLE 1

ESTIMATED MILLIGRAM EQUIVALENTS OF BENZENE METABOLIZED/DAY AS REPORTED BY SABOURIN *ET AL.* (1987) AND DERIVED MICHAELIS–MENTON CONSTANTS (K_m, V_{max})

Applied dose		Equivalents metabolized			
mg/kg	μg/liter	mg/kg	mg	K_m	V_{max}
Rat oral					
300		109.4	31.5	137	38
150		64.1	18.4		
50		34.4	9.9		
15		13.2	3.8		
5		4.7	1.35		
Mouse oral					
150		38.3	1.15	103	3
50		32.0	0.96		
15		11.7	0.35		
5		3.9	0.12		
Rat inhalation					
774	2260	117.2	33.70	339	40
172	680	48.4	13.95		
104	340	28.1	8.10		
20	75	7.8	2.25		
10	33	3.9	1.13		
Mouse inhalation					
1570	2570	144.5	4.34	495	10
159	350	97.5	2.93		
31	75	20.3	0.61		
15	29	9.8	0.29		

by surface area or metabolic rate. The authors recommended determining the appropriate scaling factor from the available data.

As shown in Table 1, at doses of 50 mg/kg and lower, 10-fold more equivalents of benzene are metabolized in rats than in mice. Since body weights were 288 and 30 g for rats and mice, respectively, the use of the allometric equation to convert from one species to another,

metabolized dose (mg) species A

$$= \text{species B dose (mg)} \times (\text{species A body wt/species B body wt})^{1},$$

is appropriate at applied oral doses of 50 mg/kg and below.

This contrasts with the situation for inhaled benzene. The milligram equivalents metabolized at various airborne concentrations, calculated with the Michaelis–Menton values, are shown in Table 2. The ratio of the metabolized dose (mg) in rats versus mice averaged 5.3, i.e., for 150 mg/kg of applied dose (or 210 ppm for rats and 120 ppm for mice), 12.24/2.33 = 5.25; and the body weight ratio of the rodents used in the pharmacokinetic studies raised to the 0.74 power indicated the same scaling, i.e.,

TABLE 2

AIRBORNE CONCENTRATIONS, APPLIED DOSE, AND MILLIGRAM BENZENE EQUIVALENTS METABOLIZED

Airborne concn (ppm)		Applied dose (mg/kg)	Milligram equivalents metabolized	
Rats	Mice		Rats	Mice
35	20	25	2.70	0.48
70	40	50	5.13	0.92
140	80	100	9.09	1.68
210	120	150	12.24	2.33
300	170	215	15.49	3.03
350	200	250	16.94	3.36
420	240	300	18.75	3.77
535	300	380	21.10	4.34

$288/30^{0.74} = 5.3$. This suggests an appropriate allometric scaling, for benzene inhalation doses, of

metabolized dose (mg) species A

$$= \text{species B dose (mg)} \times (\text{species A body wt/species B body wt})^{0.74}$$

Comparison of the information regarding half-life ($t_{1/2}$) provides further support for such scaling for inhaled benzene. In inhalation studies with rats, Rickert *et al.* (1979) found an accumulation $t_{1/2}$ in the blood of 0.7 hr. Berlin and Tunek (1984) calculated an accumulation $t_{1/2}$ of 28 hr in humans. When the $t_{1/2}$ in the rat is scaled to humans (assuming 70-kg body wt for man and 250 g for rat as given by Rickert *et al.*) with the exponent 0.67 for surface area, the predicted $t_{1/2}$ is 30 hr. This finding of a value close to the measured $t_{1/2}$ is in keeping with the conclusion by Davidson *et al.* (1986) that the $t_{1/2}$ of many compounds can be scaled in this manner. This calculation further supports the use of allometric equations based on surface area or metabolic rate for the derivation of metabolized doses in the benzene inhalation studies. While the exponent of 0.75 is generally given as the best for metabolic rate, we have chosen to use 0.74 because of its consistency with the experimental data.

ESTIMATION OF HUMAN RISK

Predicting the human cancer risk at 10 ppm (daily dose of 196 mg benzene equivalent metabolites) for the maximum occupational lifetime required estimating the human equivalent doses (HEDs) for the doses that caused the cancer response in the bioassays. The HEDs and the associated cancer responses were then used to extrapolate to the risk at a low dose, 196 mg benzene equivalents. The multistage mathematical model with the polynomial degree selected by the program for best fit (Howe *et al.*, 1986) was used for the high to low dose extrapolation.

TABLE 3

INHALATION DOSE (EXPOSURE CONCENTRATION AND MILLIGRAM EQUIVALENTS FORMED) OF BENZENE AND THE RELATED CANCER INCIDENCE IN RODENTS, THE HUMAN EQUIVALENT DOSE, AND THE ESTIMATED HUMAN RISK

Rodent dose			HED
ppm	mg eq	Cancer incidence	(mg eq)
Rat[a]		Zymbal gland	
300	26.7	4/75	903
100	11.9	2/40	405
0		1/198	
Risk in man at 10 ppm (196 mg)		0.013 (95% UCL 0.025)	
Mouse[b]		Leukemia/lymphoma	
300	5.37	8/40	1350
0		2/40	
Risk in man at 10 ppm (196 mg)		0.014 (95% UCL 0.048)	

[a] Maltoni *et al.* (1982).
[b] Snyder *et al.* (1980).

The benzene inhalation response data shown in Table 3 were used as a basis for risk assessment. Body weights of 600 and 40 g for the rats and mice, which are in keeping with information from other studies in which the same strains were used, were assumed in the absence of specific data. The doses (milligram benzene equivalents formed) at the experimental concentrations were calculated with the Michaelis–Menton constants and scaled to the HEDs with the assumed body weight ratios raised to the 0.74 power. The maximum likelihood estimate (MLE) for cancer risk in humans based on tumors of the blood-forming tissues in mice was 13 cases/1000 and the MLE for cancer risk based on tumors of the Zymbal glands in rats was 14 cases/1000.

For the risk derived from the oral bioassay data, adjustments were made for the difference in body weights for the animals used in the pharmacokinetic studies and those in the bioassay. In the NTP (1986) oral bioassay, benzene treatment caused slight reduction in the mean rodent body weights. The mean body weights at 52 weeks are given in Table 4. Because doses above 50 mg/kg were clearly above saturation, the higher dose responses were not used. The milligram benzene equivalents formed at each experimental dose were calculated with the Michaelis–Menton constants and scaled to the HEDs with the assumed body weight ratios with the exponent 1.0. The predicted response did not differ markedly from the observed responses, and the MLE risk of 6 cases/1000 with a 95% upper confidence limit (UCL) of 11 cases/1000 was comparable to the risk obtained based on the inhalation data.

DISCUSSION

The elements and results in terms of estimated human benzene risks are summarized in Table 5. The MLEs for exposure to benzene at 10 ppm for the maximum

TABLE 4

ORAL DOSE (APPLIED DOSE AND MILLIGRAM EQUIVALENTS FORMED) OF BENZENE, BODY WEIGHTS, AND THE NTP (1986) BIOASSAY ZYMBAL GLAND RESPONSE IN RODENTS, THE HUMAN EQUIVALENT DOSE, AND THE ESTIMATED HUMAN RISK

Rodent dose				
Applied (mg/kg)	Metabolite (mg eq)	Body weight (g)	Response: Observed/examined (predicted)	HED (mg eq)
	Rats male			
50	14.99	436	6/46 (0.105)	2407
0			2/32 (0.012)	
	Rats female			
50	7.94	231	5/44 (0.105)	2406
25	4.35	232	5/40 (0.0539)	1312
0			0/49 (0.012)	
	Mice male			
50	1.44	44.9	4/40 (0.0932)	2245
25	0.77	44.7	1/34 (0.0485)	1206
0			0/43 (0.012)	
	Mice female			
50	1.31	41.0	1/37 (0.0926)	2237
25	0.67	37.0	0/32 (0.0504)	1268
0			0/43 (0.012)	
	Risk in man at 10 ppm (196 mg)		0.006 (95% UCL 0.011)	

working lifetime are 6 to 14 cancer cases/1000 workers when animal data are used to make the assessment as compared to the risk of leukemia that was estimated from epidemiological studies to be 9.5 to 174 cases/1000 workers. These MLEs and their UCLs show that the estimates made with animal data closely approximate the risk predicated from epidemiological sources. The use of the scaling factors determined from the experimental data as suggested by Davidson *et al.* (1986), instead of preselected allometric procedures, leads to an agreement in the risk regardless of the route,

TABLE 5

SUMMARY OF ESTIMATED CANCER RISKS FOR LIFETIME OCCUPATIONAL EXPOSURE DAILY TO AIRBORNE BENZENE AT 10 ppm

				Risk/1000	
Subjects	Endpoint	Route	Scaling	MLE	UCL
Workers	Leukemia	Inhalation	na	9.5 to 174	—
Mice	Leukemia	Inhalation	Body $wt^{0.74}$	14	48
Rats	Zymbal gland	Inhalation	Body $wt^{0.74}$	13	25
Rats/mice	Zymbal gland	Oral	Body wt^{1}	6	11

endpoint, or species. Scaling based on surface area would have increased the risks. The illustrated agreement in estimated risks should lead to increased confidence in the assessment of risks when the principles outlined are applied.

The route-related differences in the Michaelis–Menton constants (K_m and V_{max}) may arise from the inhalation dose (substrate) being estimated as applied over a 6-hr period. This would lead to the concentration at the active site being less, not saturated, during the application of the dose. Therefore, the saturation takes place at a higher dose (substrate). As a consequence, for the oral route the same total dose applied in fractions will yield a larger amount of benzene equivalent metabolites (end product). This suggests that the oral intake of benzene in divided doses would result in a greater effect than did administration of the bolus dose as by gavage.

Much of the uncertainty in assessment of risk based on epidemiological data arises from difficulty in estimating the exposure. This uncertainty stems from exposure estimates, if available, being area exposure estimates rather than personal exposure estimates and usually being retrospective. Historically, area exposure estimates have tended to be high in the first place, and it is well known that personal monitoring generally gives lower exposure estimates than worst-case area exposure sampling data. On the other hand, the slower rate of benzene metabolism in humans would lead to accumulation with continued exposure, unlike the rapid elimination that apparently occurs in rodents. This is at least in part confirmed by the long initial $t_{1/2}$ (2.6 hr) for man calculated by Berlin and Tunek (1984) as compared to the shorter $t_{1/2}$ (0.7 hr) in rats reported by Rickert *et al.* (1979). Because of the accumulation, the estimates of human daily exposure in terms of milligram benzene equivalents of metabolites may be low for daily exposure to 10 ppm for 8 hr over a working lifetime.

Although some uncertainties still exist regarding the assessment of cancer risk from exposure to benzene, the agreement of the presented assessments supports the usefulness of animal data to estimate human risk. Risk assessment using animal bioassay data is improved when information on pharmacokinetics is available from several species. The use of across-species data to determine scaling factors is preferable over the use of predetermined factors.

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